

PALLADIUM-CATALYZED OXIDATIONS IN SELECTIVE ORGANIC SYNTHESIS

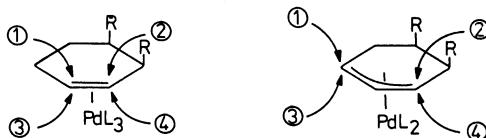
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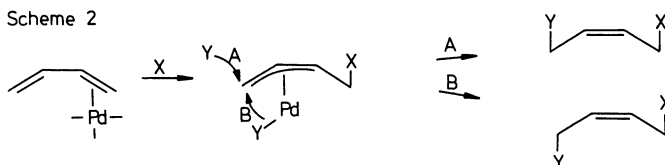
Abstract - Palladium-catalyzed oxidations of 1,3-dienes in acetic acid can be controlled to give three main reactions: 1,4-diacetoxylation, 1,4-acetoxychlorination, and 1,4-acetoxy-trifluoroacetoxylation. All three types of reactions are stereo- and regioselective and by ligand control the 1,4-diacetoxylation can be made to proceed either *cis* or *trans* across the diene. The products from these 1,4-oxidation reactions are versatile synthetic intermediates, since the chloro or carboxylate groups can be selectively functionalized. The diacetoxylation reaction was used to prepare a key intermediate for shikimic acid synthesis, and the chloro-acetoxylation was applied to pyrrole synthesis and to the synthesis of the Monarch butterfly pheromone.

Nucleophilic additions to unsaturated hydrocarbons coordinated to a transition metal are useful reactions in organic synthesis (1,2). In this way it is possible to create new carbon-carbon bonds, carbon-nitrogen bonds, carbon-oxygen bonds, and several other carbon-heteroatom bonds. In particular, nucleophilic addition to π -olefin and π -allylpalladium complexes are important processes that occur in many catalytic organic reactions. An important question in these reactions concerns the regio- and stereoselectivity of the nucleophilic attack. In principle the nucleophile may attack the hydrocarbon ligand at four different sites in each case (Scheme 1). Knowledge about the factors governing the selectivity of these nucleophilic additions is of great interest in palladium-catalyzed selective organic synthesis.

Scheme 1



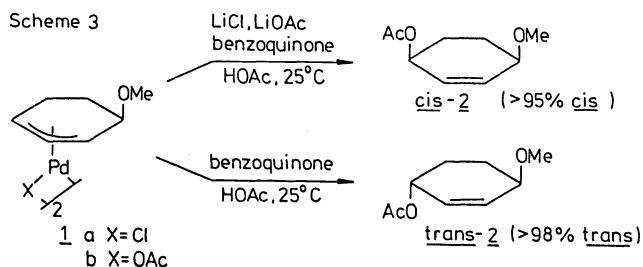
We have recently studied palladium-catalyzed 1,4-functionalizations of conjugated dienes (3,4). These reactions involve regioselective nucleophilic additions to π -olefin- and π -allylpalladium intermediates, and the principle for a 1,4-functionalization of a 1,3-diene is shown in Scheme 2. A π -allylpalladium complex is formed by a regio- and stereoselective nucleophilic attack on one of the double bonds coordinated to the metal. The introduction of



the second group is now directed to the 4-position relative to the first group. It is important to control the stereochemistry of the nucleophilic addition of the second group Y to the π -allylpalladium complex. In this way one may obtain either an overall *cis*-addition or an overall *trans*-addition across the diene.

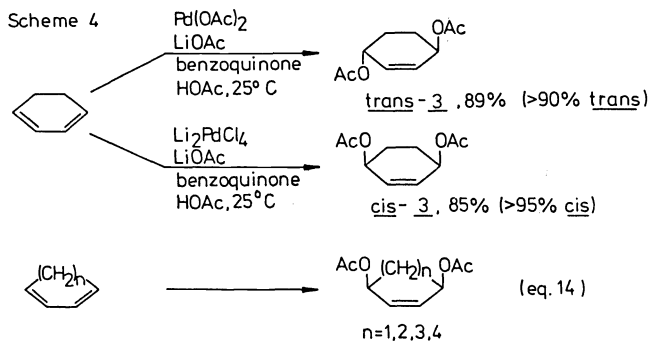
A powerful method of controlling the stereochemistry of the 1,4-addition according to Scheme 2 would be if one could direct one and a given nucleophile to selectively attack the

π -allylpalladium intermediate according to both pathways. A dilemma with this approach is that one class of nucleophiles, such as heteronucleophiles and stabilized carbon nucleophiles, prefer to attack externally (path A) (2a,5,6), whereas another class of nucleophiles, such as aryl, alkyl, and hydride nucleophiles, only attack via *cis*-migration (path B) (2a,7-9). It therefore seemed difficult to direct one nucleophile selectively towards both pathways. However, we recently demonstrated that acetate can undergo a stereoselective *cis*-migration from palladium to a coordinated allyl group (9). We later found ways of controlling the nucleophilic attack by acetate on π -allylpalladium complexes to proceed either via external *trans*-attack or via a *cis*-migration (Scheme 3) (3). Thus, acetate attack on 1 occurs by a *trans*-attack in the presence of chloride ligands, but by a *cis*-migration in the absence of chloride ligands. This stereocontrolled nucleophilic addition was also applicable to the palladium-catalyzed 1,4-diacetoxylation of conjugated dienes.

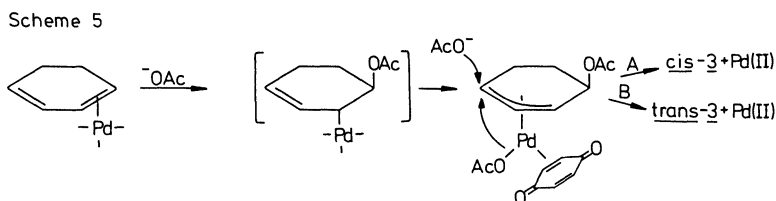


1,4-DIACETOXYLATION

1,4-Diacetoxylation of conjugated dienes takes place in good yield and high regio- and stereoselectivity (3,10). It was found that chloride and acetate ligands (as LiCl and LiOAc) have a profound effect on the stereochemical outcome of the reaction. Palladium-catalyzed oxidation of 1,3-cyclohexadiene in acetic acid in the absence of lithium salts gave a 1:1 mixture of *cis*- and *trans*-1,4-diacetoxy-2-cyclohexene. If the oxidation was performed in the presence of lithium acetate, the reaction became stereoselective and gave *trans*-3 (Scheme 4). Addition of catalytic amounts of lithium chloride had a remarkable effect on the stereochemistry. Thus, oxidation of 1,3-cyclohexadiene in the presence of lithium acetate and

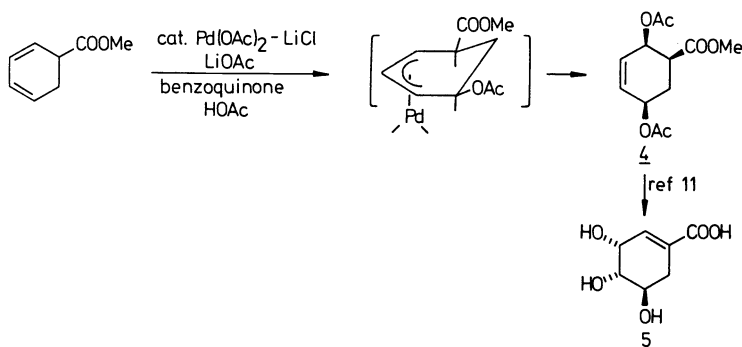


catalytic amounts of lithium chloride gave exclusively *cis*-3. The 1,4-diacetoxylation proceeds via a π -allylpalladium intermediate, which is generated *in situ* from the diene (Scheme 5). *Trans* attack or *cis*-migration produces *cis*-3 or *trans*-3 respectively. The palladium(II) salt formed by the end of the cycle coordinates another diene and starts a new cycle.



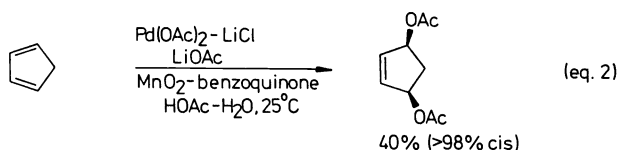
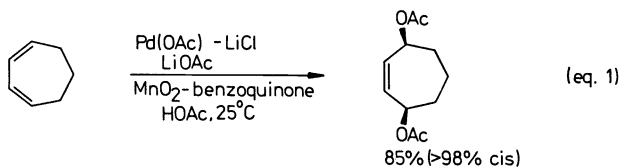
In the initial procedure of the diacetoxylation reaction we used benzoquinone as the oxidant, which in some cases resulted in an undesired competing Diels-Alder reaction between the diene and benzoquinone. We have later found that it is possible to use benzoquinone in only catalytic amounts in combination with an external oxidant such as manganese dioxide. Benzoquinone is required for the high selectivity and appears to work as a ligand.

Diacetoxylation of 5-carbomethoxy-1,3-cyclohexadiene using the "cis-diacetoxylation" procedure (catalytic amounts of LiCl) gave only the β,β,β -isomer 4 as the main product.



Compound 4 is a key intermediate for the synthesis of shikimic acid 5 (11). The reason for the stereoselectivity of the diacetoxylation in this case is probably that the most stable π -allylpalladium intermediate is formed.

The 1,4-diacetoxylation is quite general and for all cyclic dienes tried it was possible to prepare the cis-diacetates in high stereoselectivity. For example 1,3-cycloheptadiene and 1,3-cyclopentadiene gave the corresponding cis-1,4-diacetates as the only oxidation products (eqs 1 and 2). The latter diacetate is an important synthetic intermediate for natural product synthesis, in particular for prostaglandin synthesis (12).



A substituent in the 6-position of 1,3-cycloheptadiene directed the introduction of the two acetoxy groups to yield only one isomer (eq 3). Contrary to what was observed for the six-membered ring, the cis-diacetoxy groups now end up on the opposite side of the substituent.

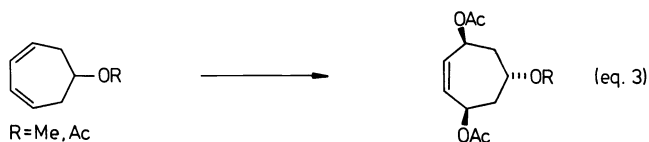
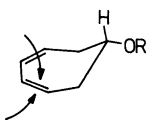


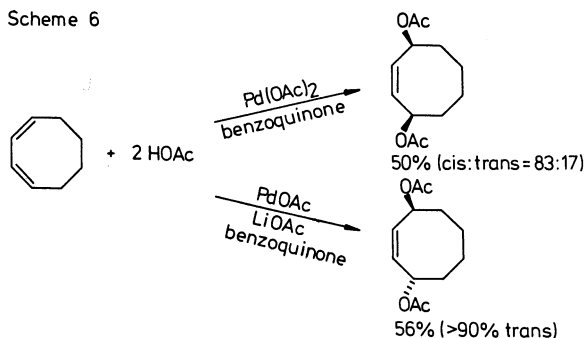
Fig. 1



less hindered exo side for metal attack

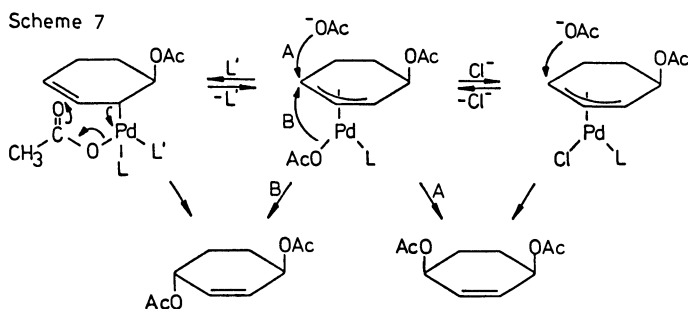
This could either be an effect of a coordination of the metal to the oxygen substituent or, more likely, a selective coordination of the metal to the less hindered side of the diene substrate (Fig 1).

For the sevenmembered ring it was not possible to completely reverse the stereochemistry towards trans-diacetoxylation. The highest relative yield of the trans-diacetate from 1,3-cycloheptadiene was 50%, which was obtained in the absence of lithium salts. For 1,3-cyclooctadiene, however, it was again possible to obtain the dual stereoselectivity for cis- or trans-diacetoxylation (Scheme 6). For this diene the stereochemistry was reversed by changing only the lithium acetate concentration in chloride free acetic acid. The presence



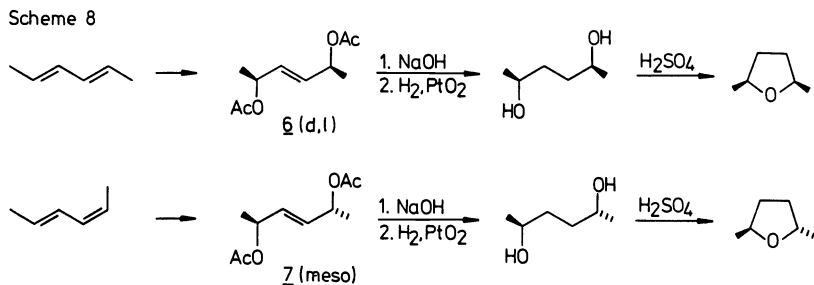
of chloride ligands also gave a very high selectivity for *cis*-addition (>98% *cis*), but there were undesired side reactions in this case, which resulted in poor chemoselectivity.

The dramatic change of stereochemistry on addition of catalytic amounts of chloride ions, which in all cases resulted in a highly stereoselective 1,4-*cis*-addition, is remarkable, and can be explained according to Scheme 7. A likely mechanism is that chloride ions effectively



block the coordination of acetate to palladium and hence hinder the *cis*-migration pathway. In the presence of chloride ligands mainly *trans*-attack on the π -allylpalladium complex takes place; in the absence of chloride ligands both *cis*- and *trans* attack can occur depending on the acetate concentration.

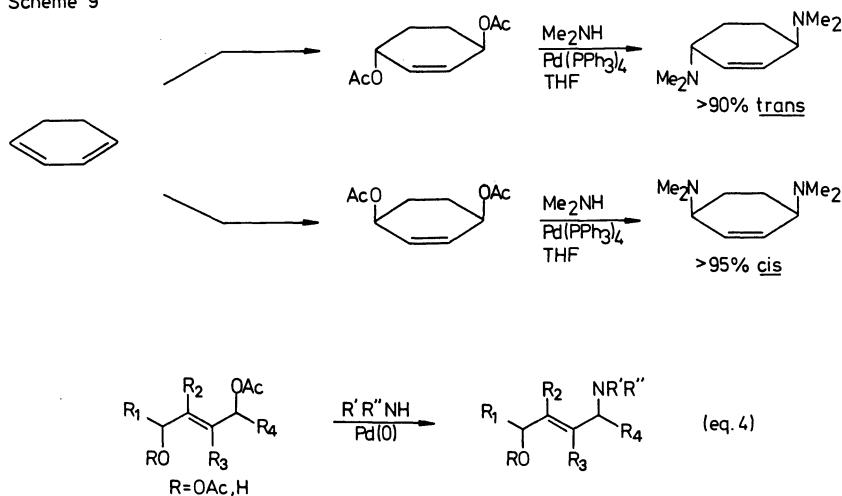
Acyclic dienes also gave a highly regiospecific palladium-catalyzed 1,4-diacetoxylation. The double bond was predominantly or only of *E*-configuration. Also in the acyclic systems it was possible to control the 1,4-relative stereochemistry between the acetoxy groups. Thus, palladium catalyzed oxidation of *E,E*- and *E,Z*-2,4-hexadiene, utilizing the procedure with chloride ligands, gave in each case one diastereoisomer as the main product, and importantly, the isomer from the *E,E*-diene differed from the one from the *E,Z*-diene. The relative configuration of the diastereoisomers **6** and **7** was determined by transformation to the corre-



sponding *cis*- and *trans*-2,5-dimethyltetrahydrofuran (Scheme 8). The diacetoxylation method therefore provides a way of controlling the relative stereochemistry at distant carbons in an acyclic system.

The products formed in these diacetoxylation reactions should be useful synthetic intermediates since allylic acetates can readily be stereospecifically substituted by a number of nucleophiles using metal catalysts (Pd, Ni, Fe, Cu) (13). One example of this is shown in Scheme 9. The example illustrates that the method indirectly allows the overall stereocontrolled 1,4-diamination of cyclic 1,3-dienes. In the acyclic series 2-alkene-1,4-diol derivatives have found application for the synthesis of vinylcyclopropane derivatives (14).

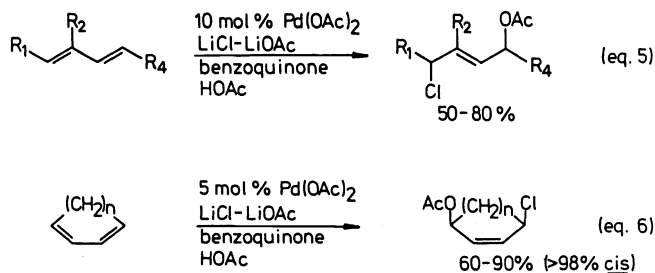
Scheme 9



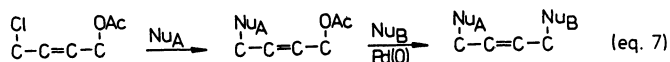
Selective palladium-catalyzed amination of acyclic 2-alken-1,4-diol diacetates or monoacetates was used as a synthetic route to 1,4-aminoalcohol derivatives (eq 4) (15).

1,4-ACETOXYCHLORINATION

If the palladium-catalyzed oxidation of 1,3-dienes in acetic acid is performed at a slightly higher chloride concentration, the product pattern changes and 1,4-chloroacetate becomes the sole product (eqs 5 and 6) (4). This reaction is highly stereospecific proceeding with overall cis-stereochemistry with cyclic dienes. The synthetic utility of the reaction is

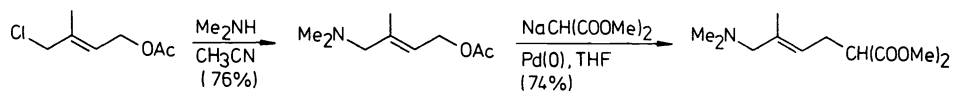


enhanced by the fact that the chloro and acetoxy groups of the product can be selectively substituted one after the other in two consecutive steps. This is achieved by using a classical nucleophilic substitution (Nu_A) followed by a metal-catalyzed nucleophilic substitution (Nu_B) of the acetoxy group (eq 7).

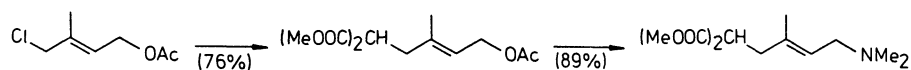


Scheme 10

A. $\text{Nu}_A = \text{Me}_2\text{NH}$, $\text{Nu}_B = \text{NaCH}(\text{COOMe})_2$:



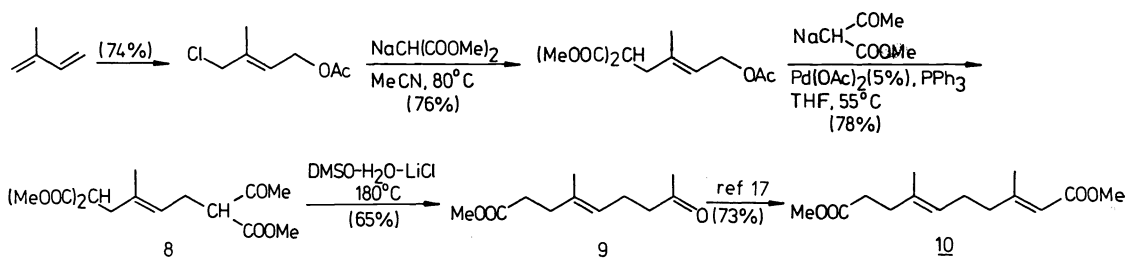
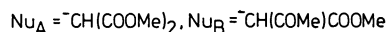
B. $\text{Nu}_A = \text{NaCH}(\text{COOMe})_2$, $\text{Nu}_B = \text{Me}_2\text{NH}$:



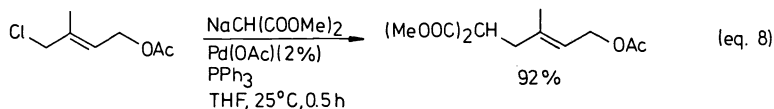
The principle is shown in Scheme 10 where the chloroacetate from isoprene is regioselectively functionalized by two different nucleophiles to the two possible regioisomers.

The chloroacetate from isoprene is a useful building block for terpenoid synthesis. We have utilized this chloroacetate for sequential dialkylation and in this way synthesized the Monarch butterfly pheromone **10** from isoprene in 5 steps (Scheme 11) (16). Using dimethylmalonate and methyl acetoacetate as Nu_A and Nu_B, respectively and substituting on the isoprene adduct gave **8**, which on selective decarboxylation afforded **9**. Since the transformation of **9** to **10** in one step has been described previously (17) the sequence in Scheme 11 constitutes a total synthesis of the pheromone from isoprene. The synthesis can be made more efficient

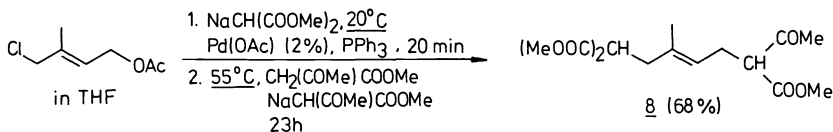
Scheme 11



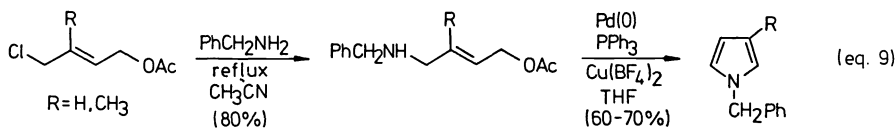
by utilizing a mild palladium-catalyzed reaction also in the first alkylation. Palladium-catalyzed substitution of the chloro group with dimethyl malonate occurred with high selectivity in high yield (eq 8). The reaction sequence is further improved by performing the two palladium-catalyzed reactions in one pot, obtaining **8** directly from the chloroacetate.



One pot procedure:

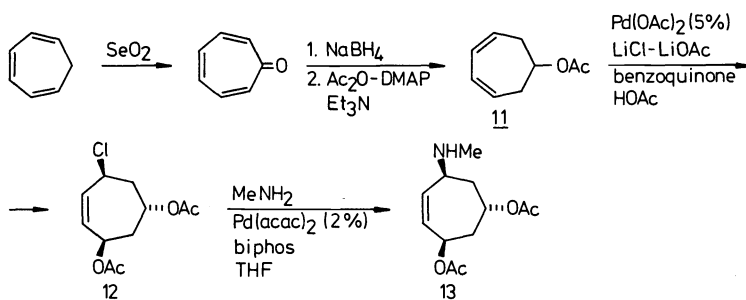


Other synthetic applications of the 1,4-acetoxychlorination include the synthesis of pyrroles (15, 18). Substitution of the chloride with primary amine followed by an intramolecular amination and subsequent oxidation gave pyrroles in good yield (eq 9).

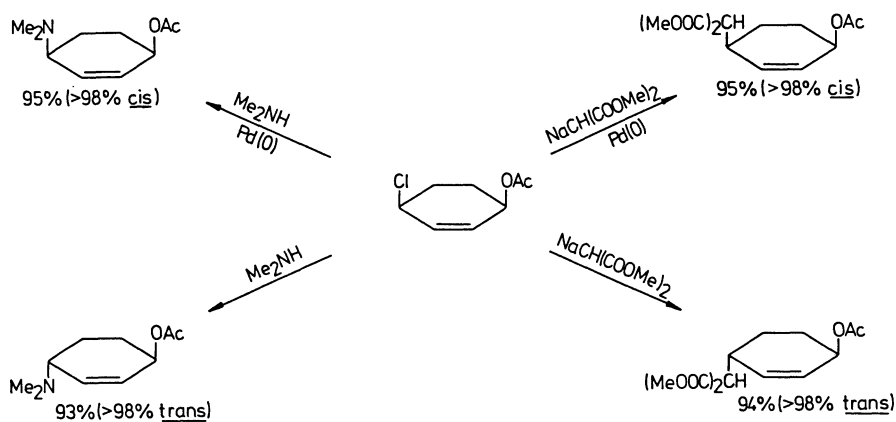


Scheme 12 outlines a stereoselective synthesis of compound **13**, which should be a useful synthetic intermediate for tropane alkaloid synthesis (19). The 1,4-acetoxychlorination of the diene **11** proceeds with high stereoselectivity and gives compound **12** as the single oxidation product. Palladium-catalyzed substitution of the chloro group with methylamine occurs with retention of configuration to give **13**. This touches upon another aspect of the chloroacetates, namely the fact that the allylic chloro group can be substituted either with retention or inversion. This was demonstrated on the chloroacetate from 1,3-cyclohexadiene. (Scheme 13) (4). A mild palladium-catalyzed nucleophilic substitution gave a product in which the chlorogroup had been replaced with complete retention of configuration at carbon. A classical nucleophilic substitution gave the inversion product. An important aspect of the products obtained in Scheme 13 is that the allylic acetoxy group can readily be stereospecifically substituted by a second nucleophile using palladium catalysis.

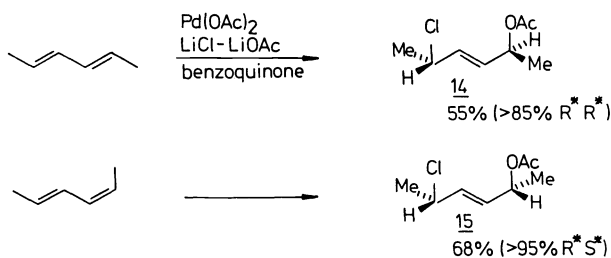
Scheme 12



Scheme 13

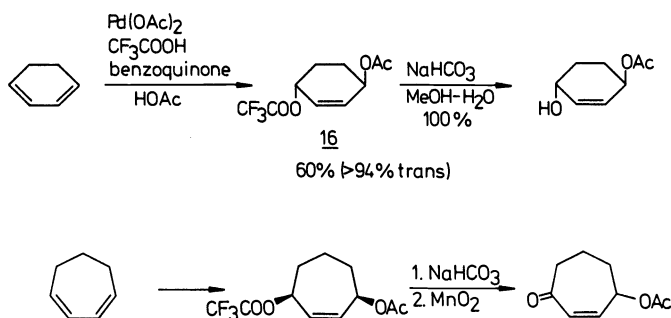


The acetoxychlorination is stereospecific also for acyclic 1,3-dienes as shown by oxidation of E,E- and E,Z-2,4-hexadiene, which gave chloroacetates 14 and 15 respectively.



1,4-ACETOXY-TRIFLUOROACETOXYLATION

Addition of stoichiometric amounts of trifluoroacetic acid to the palladium catalyzed oxidation of 1,3-cyclohexadiene in salt free acetic acid resulted in the formation of a new product. This product was the unsymmetrical 1-acetoxy-4-trifluoroacetoxy-2-cyclohexene 16 of trans configuration (20). The selectivity for unsymmetrical product was not complete in this case and the ratio diacetate : 16 : bis-trifluoroacetate was approximately 1 : 20 : 3. A cis-migration of coordinated trifluoroacetate from palladium to carbon in an intermediate π -allylpalladium complex would account for the observed stereochemistry. 1,3-Cycloheptadiene



gave a stereospecific overall *cis*-addition (>97% *cis*) of the acetoxy and trifluoroacetoxy groups. Selective hydrolysis of these unsymmetrical dicarboxylates afforded 2-cycloalken-1,4-diol monoacetates, which could be oxidized to the corresponding 4-acetoxy-2-cycloalkenones. The latter compounds are useful synthetic intermediates as masked diketones.

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